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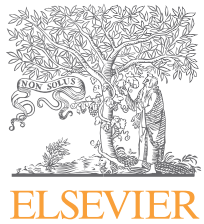

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EORTC Gynecological Cancer Group on the frontline of practice-changing clinical trials

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ABSTRACT

After more than 30 years of clinical and translational research, and having contributed to large randomized international clinical trials in gynecologic cancer, the multidisciplinary EORTC Gynecologic Cancer Group (GCG) currently is dealing with one of the greatest challenges in cancer research, which is to discover and establish clinically useful predictive and prognostic factors, to identify subgroups of patients based on genomic patterns and activated pathways and to design clinical trials appropriate for such subgroups. EORTC GCG current and future research has to include the validation of prognostic and predictive markers, the identification of novel therapies that target specific pathways, and a better understanding of the molecular basis for resistance. These studies will require the collection of large numbers of biologic specimens, both at time of diagnosis and at time of recurrence and, whenever possible, during treatment. These objectives can only be reached with transversal cooperation within the EORTC framework (Pathobiology group, Imaging group, etc.), as well as international cooperation. Support from private industry will also be important in the context of a high-standard cooperation among industry and academia. The EORTC with its unique multidisciplinary infrastructure and long experience in cancer research is taking part through the EORTC GCG in international

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networks focused on gynecological cancer research on a large scale. Intergroup collaboration and international contribution to establish the current and future world-wide standards of care is also a priority for the GCG. The GCG also has a good track record in rare tumors and will continue working on rare diseases along with international partners.

1. Introduction

The EORTC Gynecological Cancer Group (GCG) is a multidisciplinary clinical disease oriented group composed of gynecological oncologists, clinical/medical oncologists, scientists, radiation oncologists and pathologists together with a number of data managers/trial coordinators and nurses from 92 centers across Europe and other countries. The GCG has conducted more than 60 large clinical trials in a variety of gynecological cancers over the last 35 years (Figs. 1,2). This paper will highlight the most marking trials conducted by the GCG that have played, and will play, a significant role in the field of (therapy innovation for) gynecological cancers.

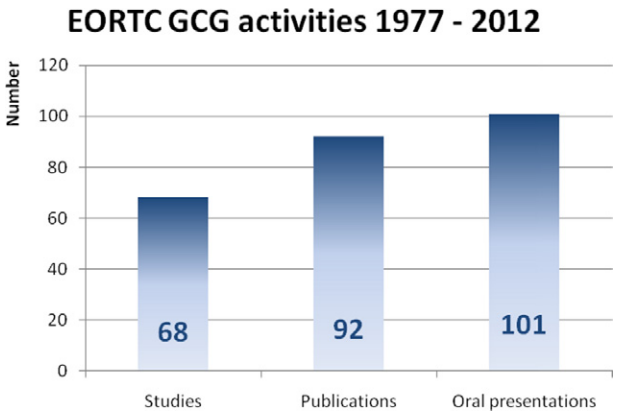

Fig. 1 – Summary of GCG scientific activities over the period 1977–2012. The number of studies includes six trials (55092, 55102, 55111 and three initiatives in rare tumors) recently opened or soon to be opened in 2012. The number of publications includes peer-reviewed articles only. Representation at important congresses is reflected by the number of oral presentations.

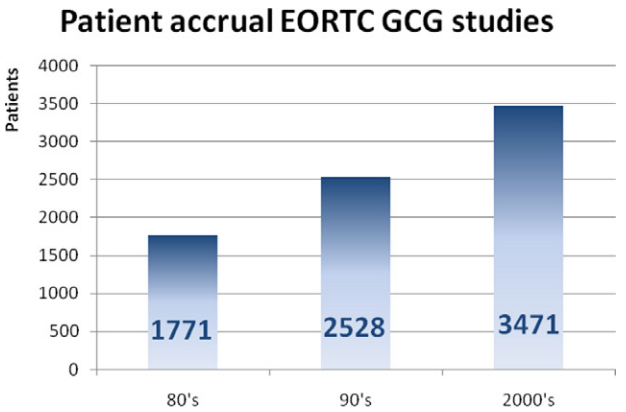

Fig. 2 – Patient accrual in GCG studies is presented per decade and includes recruitment numbers from other collaborative groups in case of intergroup trials.

2. Ovarian cancer

2.1. Adjuvant chemotherapy in early-stage ovarian cancer patients

Whilst some important studies were carried out in the 1980's it was really in the 1990's that significant protocols came into being which led to an impact on treatment delivery. Arguably one of the most important of these was the **ACTION Study (EORTC 55904)** which investigated the role of adjuvant chemotherapy in early ovarian cancer. The ACTION study was a randomized clinical trial in 448 early ovarian cancer patients, International Federation of Gynecology and Obstetrics (FIGO) stage I and IIa, comparing adjuvant chemotherapy to no further treatment after surgery. In the original analysis, adjuvant chemotherapy improved recurrence-free survival (RFS) but not overall survival (OS).[1] The patients who received adjuvant chemotherapy had better RFS than patients who were allocated to the observation arm, with a hazard ratio (HR) equal to 0.63 (95% CI: 0.43–0.92, p = 0.02). A similar trial carried out by the Medical Research Council (MRC), the ICON-1 study, demonstrated that women with early-stage epithelial ovarian cancer who received adjuvant chemotherapy had better RFS and OS than women who did not.[2] A pre-planned combined analysis of these two parallel randomized clinical trials (ACTION and ICON-1) was published in 2003. In this analysis, the improvement in RFS and OS after adjuvant chemotherapy was confirmed. A total of 924 patients were randomized. With over four years median follow up for survivors, the HR for RFS was 0.64 (95% CI: 0.50–0.82; P = 0.001) in favor of adjuvant chemotherapy, with an absolute difference of 11%. For OS, the HR was 0.67 (95% CI: 0.50–0.90; P = 0.008) in favor of adjuvant chemotherapy. These results translated into an absolute difference of 8% in the adjuvant chemotherapy group, and indicated that adjuvant platinum-containing chemotherapy improved

survival and disease-free survival. Subgroup analysis provided no evidence of a difference in the size of effect of chemotherapy on survival in any pretreatment subcategory. [3]

In the ACTION study, subgroup analysis showed that the completeness of surgical staging was an independent prognostic factor and that the benefit of adjuvant chemotherapy was mainly limited to patients who underwent incomplete (non-optimal) surgical staging. [1] The long-term analysis with a median follow-up of 10.1 years confirmed the main conclusions of the original analysis. [4] A benefit but no cancer-specific survival benefit of adjuvant chemotherapy was seen for the whole ACTION study group. Completeness of surgical staging in patients with early-stage ovarian cancer was found to be statistically significantly associated with better outcome in the both the control and the chemotherapy group. The benefit from adjuvant chemotherapy in terms of overall and RFS appeared to be most evident in patients with non-optimal surgical staging, and this held as well for patients with a grade 3 tumor. [1,4] There has been some debate about the interpretation of the sub-analyses of the ACTION trial. There remains discussion about whether chemotherapy can be omitted in patients with optimally staged early-stage ovarian cancer. Although the benefit from adjuvant chemotherapy appeared to be predominantly effective in patients with non-optimal surgical staging, presumably because these patients have more risk of harboring unappreciated residual disease, this subgroup analysis has to be interpreted with caution. The limited sample size and the fact that the ACTION trial was not specifically designed to compare different surgical staging categories – the patients were not prospectively stratified according to the various surgical staging categories – cannot rule out a benefit from chemotherapy in the optimally staged patients.

2.2. Interval debulking surgery and neoadjuvant chemotherapy in stage IIIC–IV ovarian cancer patients

The other important relatively early study within the GCG was the **Interval Debulking Study (IDS)** in Ovarian Cancer **(EORTC 55865).** This clinical trial included FIGO stage IIb–IV patients and randomized patients with residual disease either to complete $\geqslant$6 cycles of chemotherapy or 3 cycles of chemotherapy followed by interval debulking surgery and additional $\geqslant$3 cycles of chemotherapy. This study showed, and continues to show with over 10 years follow up, that there is a significant survival advantage to the patients who underwent IDS [5] (Fig. 3). This has been disputed by some, particularly as the GOG 158 protocol in the USA showed no benefit of interval debulking surgery. However there were some significant differences in the entry criteria and also the specialization of the surgeon. In the GOG study all patients were operated by gynecological oncologists but in the EORTC there was

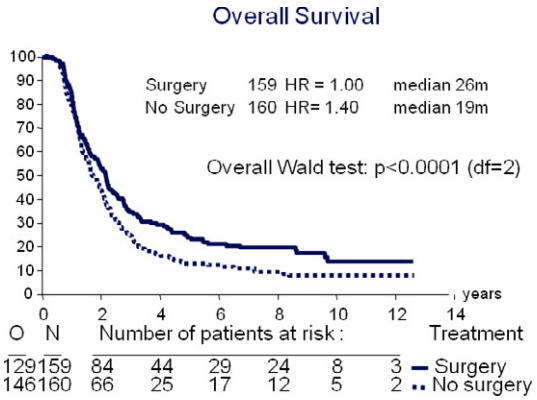

Fig. 3 – Survival curve for patients who underwent debulking surgery and for those who did not (figure published by courtesy of van der Burg).

a mixture of general gynecologists and gynecological oncologists. In addition, in GOG 158 a maximal surgical effort at primary surgery was required for inclusion, which was not needed for inclusion in the EORTC study. Many oncologists have interpreted these results as showing that when an initial surgery has been performed by a gynecological oncologist then IDS probably has a minimal role to play, in all other cases interval debulking surgery is of benefit. This study also has helped to promote referral of women with gynecological cancers to specialist gynecological oncologists.

In September 2010 the **EORTC 55971/NCIC-CTG OV13 trial** (conventional surgery followed by chemotherapy with or without interval debulking was compared with neoadjuvant chemotherapy and delayed primary surgery in stage IIIC and stage IV ovarian cancer) was honored with a landmark paper from Dr Ignace Vergote and EORTC/NCI-C collaborators in the *New England Journal of Medicine*. [6] The importance of primary cytoreductive surgery in the treatment of advanced ovarian cancer FIGO stage IIIc and IV was already suggested as early as 1934, but it was not until the 1970's that the amount of residual tumor following primary surgery was shown to be an important prognostic factor in advanced ovarian carcinoma. Leaving no residual tumor following primary debulking surgery has been shown to be the single most important independent prognostic factor in advanced ovarian carcinoma in many prospective and retrospective studies.

Recently, many institutions have switched to using neoadjuvant chemotherapy in patients with advanced ovarian cancer (without primary attempt of debulking) followed by an interval debulking surgery (usually after three courses of chemotherapy). The advantages of neoadjuvant chemotherapy include an increased rate of optimal surgery, reduced blood loss, lower morbidity, shortened hospital stay, improved quality of life, and acting as a mechanism to select out

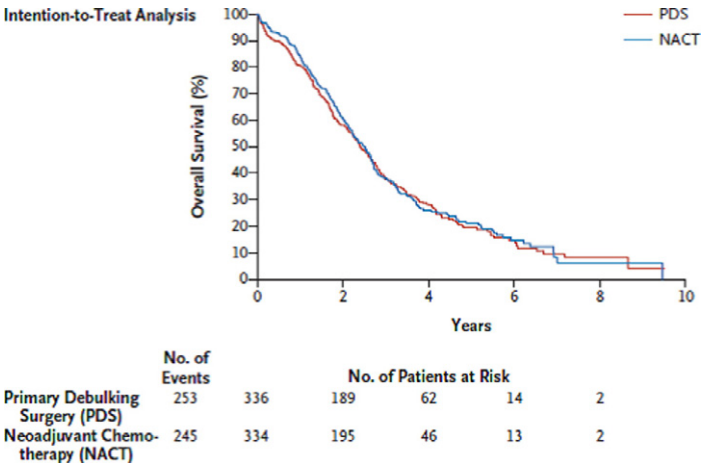

Fig. 4 – Kaplan–Meier plot for overall survival in neoadjuvant chemotherapy or primary surgery in Stage IIIc and IV ovarian cancer (EORTC 55971). [6]

patients with platinum resistance. Although there was evidence from retrospective studies that neoadjuvant chemotherapy followed by interval debulking surgery was a valid alternative in a selected group of patients with stage IIIc or IV ovarian carcinoma, this was only recently confirmed in this prospective randomized trial performed by the EORTC-GCG in cooperation with the NCIC-CTG. The objective of the EORTC-GCG 55971/INCIC-CTG trial 0VO16 was to compare primary debulking surgery (PDS) followed by $\geqslant$6 courses of platin-based chemotherapy (CT) (Arm A) with 3 courses of neoadjuvant chemotherapy (NACT), interval debulking surgery (IDS) and another $\geqslant$3 courses of CT (Arm B) in Stage IIIc–IV ovarian, fallopian tube or peritoneal carcinoma (OVCA). To be eligible the patients needed to have biopsy-proven OVCA; or fine needle aspiration suggesting the presence of OVCA, in combination with a pelvic mass, presence of metastases of $\geqslant$2 cm outside the pelvis and a CA125:CEA ratio $\geqslant$25. Non-inferiority for OS (one-sided type I error 0.05, power 80%) required 704 patients.

Between September 1998 and December 2006, 718 patients were randomized. The baseline characteristics for arms A and B were similar. The intention to treat analysis showed a similar OS (Fig. 4) and progression-free survival (PFS). The per- and post-operative complications were lower in the neoadjuvant arm than in the primary debulking arm. In the multivariate analyses complete resection of all macroscopic lesions was the strongest independent prognostic factor for OS. The timing of this procedure (PDS or IDS) did not seem to play a role in the group of patients as included in the study. In this respect it should be mentioned that most patients included in this trial had an extensive stage IIIc–IV disease. This study showed that neoadjuvant chemotherapy followed by interval debulking surgery is a good alternative for primary debulking surgery in patients with extensive stage IIIc or IV ovarian carcinoma, as included in the study. Less per- and post-operative complications were observed in the neoadjuvant arm compared to the primary debulking arm. [6] The results of the trial are not applicable to patients with lower stage disease (IIb–IIIb). Furthermore, the authors highlighted that in patients with a relatively limited stage IIIc or IV disease, which can easily be resected to no residual tumor, primary debulking surgery remains the preferred recommended option.

Based on this platform, the EORTC GCG is looking at a newly comprehensive trial in which novel targeted agents can be tested in this group of patients with Stage IIIc and IV disease. There is a unique opportunity to collect tissue specimens before and after therapy and also to evaluate complex functional imaging techniques.

2.3. CA125 intervention study in collaboration with the MRC/NCRI

Results of another practice-changing trial, **MRC 0VO5/EORTC 55955**, a randomized trial in relapsed ovarian cancer of early treatment based on confirmed elevation of CA125 versus delayed treatment based on clinical relapse, were recently published. [7] Serum CA125 often rises several months before women with ovarian cancer have clinical/symptomatic relapse. MRC OV05/EORTC 55955 investigated whether there were benefits from early treatment based on confirmed elevation of CA125 versus delaying treatment until clinically indicated. Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125 were registered. Every 3 months CA125 was measured and monitored by coordinating centers, and a general and gynecological examination was performed; patients and investigators were blinded to CA125 results. If CA125 levels exceeded twice the upper limit of normal, patients were randomized to early

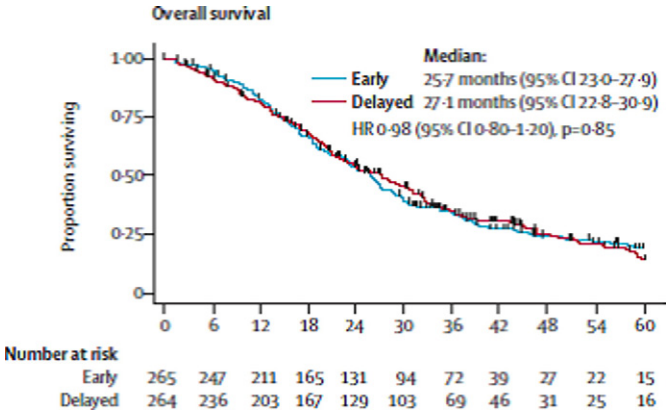

Fig. 5 – Kaplan–Meier plot for overall survival in early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955). [7]

chemotherapy or delayed chemotherapy (continuing blinded CA125 with treatment commencing if clinical/symptomatic recurrence). All patients were treated according to standard local practice. 1442 patients were registered and 529 randomized (265 early, 264 delayed). The EORTC GCG contributed substantially to this study with 298 patients included. Baseline characteristics were well balanced between randomized groups; their median age at registration was 61 years; 81% had FIGO stage III/IV disease. Second-line and third-line chemotherapy started a median of 4.8 months and 4.6 months sooner in the early arm. With a median follow up of 56.9 months from randomization and 370 deaths, there was no evidence of a difference in OS between the early and delayed arms (Fig. 5), HR = 0.98 (95% CI: 0.80–1.20), p = 0.85, nor improvement in quality of life.

The conclusion was that there is no evidence of a survival benefit or better quality of life with early treatment of relapse based on a raised CA125 level alone, and therefore no value in the routine measurement of CA125 in the follow-up of ovarian cancer patients who attain a complete response after first-line treatment. This is the most solid evidence coming from a randomized trial; however, we have to take into account some limitations: in this study the role of secondary cytoreduction was not considered. In the near future, a better understanding of ovarian cancer biology, more sensitive diagnostic techniques, more accurate surgical procedures along with the availability of new compounds will probably improve prognosis. In this scenario, the anticipation of salvage therapy might play a different role. In addition, the role of treatment on the basis of CA125 increase at second or later relapse needs to be established.

2.4. Other highlights in ovarian cancer

The EORTC GCG conducted the first targeted agent maintenance trial amongst all EORTC disease groups (EORTC 55041). An extensive part consists of translational research in this trial where a comparison between two years of daily erlotinib versus observation is made in patients with no evidence of disease progression after first-line, platinum-based chemotherapy for high-risk stage I and stage II–IV ovarian epithelial, primary peritoneal, or fallopian tube cancer. The results of this intergroup randomized trial are expected to be published soon.

In a randomized phase III European–Canadian intergroup trial in first-line setting (EORTC 55931) where cisplatin–paclitaxel was compared to cisplatin–cyclophosphamide, a significant improvement for the paclitaxel regimen was shown in PFS and OS, confirming the GOG111 study results. [8] In addition, the survival superiority of the paclitaxel regimen was confirmed in the long-term follow up results. [9]

Worthwhile to mention are certainly a few trials conducted by the group which failed to secure their assumptions of changing treatment standards. The randomized phase III trial in first-line setting in which sequential cisplatin/topotecan followed by paclitaxel/carboplatin was compared with paclitaxel/carboplatin only therapy – EORTC 55012/NCIC-CTG OV16/GEICO-001 led by the Canadian group – has recently published the results of the PFS primary endpoint. The conclusion of this trial with 819 patients with advanced epithelial ovarian cancer was that sequential therapy was more toxic than the standard arm, without improved efficacy. [10] The next analysis with the required 631 events for OS will be carried out in due time.

In another trial (EORTC 55875: Intraperitoneal cisplatin versus no further treatment: A phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based induction chemotherapy and cytoreductive surgery) intraperitoneal chemotherapy as consolidation therapy was not different (both PFS and OS) compared to observation and as such did not support a change in clinical practice. [11]

Another interesting trial was the LOROCSON study (EORTC 55963: A randomized phase III study in Late Onset

Table 1 – Treatment optimization trials in cervix cancer (published EORTC studies)

#	Study title	Eligible patients	Main results
55802 [12]	Phase II trial of vincristine, bleomycin, mitomycin C and cisplatin (VBMP) in disseminated squamous cell carcinoma of the uterine cervix	50	Response: 40% median survival 37 wks
55832 [13]	Phase II study of mitomycin C - cisplatin in disseminated squamous cell carcinoma of the uterine cervix	33	ORR: 42% median duration 7.9 mo
55851 [14]	Phase II trial of a combination of vindesine, cisplatin, bleomycin, and mitomycin-C (BEMP) in disseminated squamous cell carcinoma of the uterine cervix	161	ORR: 45% median duration 7.6 mo Best prognosis in pts with good PS and only metastatic disease
55863 [15]	Randomized phase III trial of vindesine, cisplatin, bleomycin and mitomycin-C (BEMP) versus cisplatin (P) in disseminated squamous cell carcinoma of the uterine cervix	235	BEMP vs. P ORR: 45% vs. 25% OS: 10.1 vs. 9.3 mo (NS) BEMP: higher toxicity
55835 [16]	Phase II study of bromocriptine in the treatment of patients with carcinoma of the cervix	18	ORR: 28%
55842 [17]	Phase II trial of 4′-epiDoxorubicin in disseminated carcinoma of the uterine cervix	24	Partial Response: 4% median duration 23 wks
55857 [18]	Phase II trial of 5-aza-2′-deoxycytidine in patients with advanced or recurrent squamous cell carcinoma of the uterine cervix	15	No remission
55883 [19]	Phase II study of Navelbine in patients with advanced and/or recurrent cervical carcinoma	41	Partial Response: 17% median duration 5 mo

Recurrent Ovarian Cancer: Surgery Or Not; patients were randomized between chemotherapy with or without IDS), probably ahead of its time and a regrettable lost opportunity to lead the world with treatment modality trial(s). The concept of this trial was picked up by the German national group and the DESKTOP trial series is currently successfully recruiting.

3. Cervix carcinoma

The GCG has a long history of successful trials in cervical cancer and is finalizing a randomized phase III study of neoadjuvant chemotherapy followed by surgery *versus* concomitant radiotherapy and chemotherapy in FIGO Ib2, IIa >4 cm or IIb cervical cancer (EORTC 55994). This trial is of utmost importance as today the scientific community is eager to learn about the best treatment modality in this early-stage population.

Not all of these trials have led to practice-changing treatments and some investigational therapies were found to be inactive in this disease. However, the trials listed in Table 1, some in collaboration with other groups, demonstrate that the GCG has invested much effort in optimizing treatments especially in advanced metastatic cervical cancer.

4. Corpus tumors

Tumors of the uterus have been explored by the GCG over the last decades. Most of these trials were pure academic trials, but remarkably these trials were done with great enthusiasm and quality amongst the different members.

An ambitious trial initially conceived by Dr Nina Einhorn and completed by Dr Nick Reed and colleagues is certainly the work in uterine sarcomas. The role of post-surgical radiotherapy has long remained controversial in the management of this disease. The EORTC performed a randomized phase III trial in stage I and II uterine sarcomas to evaluate a potential benefit of adjuvant radiotherapy in this population. Over a 13-year period, this study recruited 224 patients including 103 leiomyosarcomas (LMS) followed by 91 carcinosarcomas (CS) and 28 endometrial stromal sarcomas. The benefit in local control for CS (not seen in LMS) did not translate into any difference in OS between immediate post-operative pelvic radiotherapy and observation. These results clearly demonstrated that women with uterine sarcomas can be spared adjuvant radiotherapy. [20]

The group studied different chemotherapy regimens in advanced and/or recurrent endometrial cancer (EORTC trials 55872, 55873 and 55984). The combination regimen of adriamycin/cisplatin was superior to adriamycin alone with a modest survival benefit, [21] and the trial with second-line cyclophosphamide versus ifosfamide – showing superiority of the latter – demonstrated that cyclophosphamide was not an active drug at all for this disease. [22] The results of the trial comparing TAP *versus* AP are expected to be published.

A cornerstone of endometrial carcinoma treatment consists of radical hysterectomy and bilateral salpingectomy and oophorectomy (BSO) followed by adjuvant

Table 2 – EORTC GCG involvement in rare gynecological tumors

Disease	EORTC trial number(s)	Eligible patients
Advanced vulvar cancer [33–35]	55831, 55871, 55985	85
Granulosa theca cell tumor [36]	55843	38
Uterine sarcomas (LMS, CS, ESS) [20]	55874	224
Carcinosarcoma (malignant mixed mesodermal tumors) [37]	55923	41
Dysgerminoma [38]	55862	18
Clear cell carcinoma in early ovarian cancer [39]	55904 – ACTION	63

treatment in case of high risk of recurrences. To avoid over- and under-treatment, it is extremely important to know the different risk factors and the effect of post-operative radiotherapy, chemotherapy, and hormonotherapy. The problem is that even today, appropriate tailoring for each woman is not possible due to controversies which exist for some treatments. Further research is required to find optimal treatment with emphasis on survival and quality of life. [23] In response to the current lack of a consensus approach in endometrial cancer, various academic institutions discussed and analyzed the pertinent problems in the treatment of women with endometrial cancer and designed the NEtwork STudy in Endometrial Cancer (NESTEC). This academic platform will try to answer four main questions: (1) Does proper lymph node excision improve survival? (2) Is there a need for post-operative chemotherapy in high-risk early-stage patients without metastasis to the lymph nodes? (3) Is post-operative chemotherapy followed by radiation therapy better than chemotherapy alone in high-risk early-stage patients with unknown lymph node involvement? (4) Are new chemotherapeutic regimens better than the standard combination chemotherapy in prolonging survival of advanced/relapsed disease? The EORTC GCG is on the verge to start the 55102 trial (A phase III trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I–II intermediate or high risk endometrial cancer) in collaboration with the Danish Gynecological Cancer Group and other European Network of Gynecological Oncological Trial (ENGOT) groups in order to answer the second question.

Collaboration with the EORTC Quality of Life Group resulted in the publication in 2011 of the validated endometrial module (QLQ-EN24) questionnaire, a supplement to the EORTC QLQ-C30 core questionnaire developed by Dr Eva Greimel and her group. [24] The EORTC 55102 trial will be the first phase III trial implementing this endometrial module. Similar validated supplemental modules for ovarian (QLQ-OV28) and cervical (QLQ-CX24) cancer were published respectively in 2003 and 2006. [25,26] Together with the GCG members a new vulva cancer QoL module is currently under development.

5. Translational research

The group has a very good track record of translational research projects, certainly in the merit of Dr John Green, with publications dating back to 1997. [27] Currently the GCG TR committee is chaired by Dr Els Berns and Dr Maria van der Burg, who have expanded the portfolio of projects in the last years.

Two GCG translational research applications were awarded in 2008 and 2009 during the EORTC strategy meetings. The results of the first one, from Dr Jozien Helleman and Dr Els Berns, "Towards ovarian cancer specific predictive signatures", are currently submitted for publication. A combined prognostic and predictive assessment on the EORTC 55041 study is performed by pharmacogenomic and immunohistochemical evaluation of the EGFR pathway in ovarian cancer patients treated with erlotinib in the 2009 awarded work, "genetic signatures for prediction of platinum-sensitivity in ovarian cancer" by Dr Evelyn Despierre and Dr Ignace Vergote.

6. Quality control and quality assurance

A quality control and assurance program has been established within different gynecological tumor domains. Several papers have been published looking at general approach of the gynecological oncology population [28,29] as well as specific topics, such as quality indicators of radical hysterectomy in cervical and ovarian cancer and the impact of the quality of pathology reports on cancer care. [30–32]

7. Rare tumors

As mentioned earlier, the GCG has been on the frontline in cutting-edge clinical trials and has a profound curriculum in rare gynecological tumors. Table 2 summarizes the published EORTC trials within different rare tumors. Most of the publications prior

to these EORTC studies were based upon case studies, therefore special acknowledgement is reserved for these successful recruitment numbers and scientific contributions towards a better understanding of the disease as well as treatment optimization. Sadly, due to changes in EU regulations, it is very challenging to perform studies in these rare cancers unless they are supported by the pharmaceutical industry. The GCG would be well placed to take the lead in coordinating and running these trials within Europe if it were given the support to do so.

The GCG has played an instrumental role in the set up of the Gynecologic Cancer Intergroup (GCIG). Not only has the contribution over the years been crucial, but also the fact that the group played a leading role in its development, which is illustrated by the effort of its first Chair, Dr Jan Vermorken. Today, the GCIG is an important platform by which new treatment options can be brought to the patients in a much more rapid manner. [40,41] The GCG is a vigorous contributor to ENGOT to streamline and exchange creative ideas on performing clinical trials between different collaborative groups. Recently, the group was an active participant of the newly established NCI/NCRN/EORTC International Rare Cancers Initiative (IRCI). The latter cooperation led to a portfolio of three possible clinical trials in gynecological sarcomas which are, due its nature, only feasible to run on a global level. The study proposals under development are within the following diseases: early-stage high-grade uLMS, high-grade uterine sarcoma, and low-grade ESS and uLMS.

8. Current and future activities

The EORTC translational and imaging research processes are now well established, and most of the future GCG studies will provide the basis for molecular approaches to the management of patients with gynecological cancers. The group is currently focusing on identifying top areas (targets, surgical or radiation issues) for future clinical trials. Intergroup collaboration and international contribution to establish the current and future world-wide standards of care for patients with gynecological malignancies is also a priority for the GCG. Finally the GCG is well placed to be the key liaison for conducting rare tumor trials and studies if given the resources and support.

9. Conflict of interest statement

Bjorn Penninckx, Corneel Coens, Annamaria Ferrero, Els M.J.J. Berns, Ignace Vergote, Fernando Mota, Jan Vermorken, Antonio Jimeno, Dionyssios Katsaros, Maria E.L. van der Burg, Antonio Casado and Sergio Pecorelli declare no conflicts of interest. Nicholas Reed consulted for Novartis, Schering-Plough, BMS, Roche, Otsuka, and Johnson & Johnson.

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